

# Endogenous plasma endothelin concentrations and coronary circulation in patients with mild dilated cardiomyopathy

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## Abstract

**Objective**—To determine whether increased plasma concentrations of endothelin-1 (ET-1) and big endothelin (BET) play a role in the regulation of coronary circulation in patients with idiopathic dilated cardiomyopathy (IDCM).

**Setting**—Tertiary referral centre for cardiac diseases.

**Patients**—Fourteen patients (eight male/six female; mean (SD) age 59 (9) years) with IDCM (ejection fraction 36 (9)%) and five normotensive subjects (two male/three female; age 52 (7) years) serving as controls were studied.

**Methods**—Functional status was classified according to New York Heart Association (NYHA) class. Endogenous ET-1 and BET plasma concentrations from the aorta and the coronary sinus were determined by radioimmunoassay. Coronary blood flow, using the inert chromatographic argon method, myocardial oxygen consumption, and coronary sinus oxygen content under basal conditions were determined.

**Results**—In the aorta, mean (SD) concentrations of ET-1 (IDCM 0.76 (0.25) v controls 0.31 (0.06) fmol/ml;  $p = 0.002$ ) and BET (IDCM 3.58 (1.06) v controls 2.11 (0.58) fmol/ml;  $p = 0.014$ ) were increased in patients with IDCM. Aortic ET-1 concentrations correlated positively with NYHA class ( $r = 0.731$ ;  $p < 0.001$ ), myocardial oxygen consumption ( $r = 0.749$ ;  $p < 0.001$ ), and coronary blood flow ( $r = 0.645$ ;  $p = 0.003$ ), but inversely with coronary sinus oxygen content ( $r = -0.633$ ;  $p = 0.004$ ), which was significantly decreased in IDCM patients (IDCM 4.68 (1.05) v controls 6.70 (1.06) vol%;  $p = 0.003$ ).

**Conclusions**—The coronary circulation in patients with IDCM is exposed to an increased endothelin load. ET-1 concentrations correlate with functional deterioration. A decrease of the coronary sinus content of oxygen suggests a mismatch between coronary blood flow and metabolic demand. Thus, ET-1 might be a marker of a disequilibrium between myocardial oxygen demand and coronary blood flow in IDCM.

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Endothelin-1 (ET-1), a 21 amino acid residue originally characterised by Yanagisawa and colleagues,<sup>1</sup> acts via specific receptors and has both vasoactive as well as mitogenic effects.<sup>2–3</sup> In recent years, raised plasma concentrations of ET-1 have been described in different forms of heart disease, and its role in heart failure is currently being investigated.<sup>4–6</sup> Different studies<sup>7–8</sup> have shown that the activation of the endothelin system is associated with a poor prognosis in idiopathic dilated cardiomyopathy (IDCM) and chronic congestive heart failure (CHF). However, the pathophysiological role of raised plasma ET-1 and big endothelin (BET) concentrations in the progression of CHF in IDCM is unknown. A recently published study in humans provided evidence of a major contribution of endothelin towards maintaining an increased peripheral vascular tone in CHF.<sup>9</sup> On the other hand ET-1 has positive inotropic effects that may initially compensate reduced contractility in CHF,<sup>10</sup> but may decrease cardiac performance at cellular and haemodynamic levels in the long term.<sup>11–12</sup> Thus, adaptive at first, the endothelin system eventually contributes to the progression of CHF.

Most investigations on the haemodynamic effects of the endothelin system in humans were carried out in relation to systemic or pulmonary vascular beds,<sup>9–13</sup> while there are few data about coronary vascular effects in normal or diseased human hearts.<sup>14–15</sup> It is unclear whether the heart in IDCM is exposed to a higher than normal circulating plasma ET-1/BET load or if ET-1/BET is substantially released from the myocardium into the coronary sinus under basal conditions.

This study aimed to determine the arterial and coronary sinus ET-1 and BET plasma concentrations, as well as coronary blood flow and myocardial oxygen consumption, in patients with mild IDCM.

## Methods

### PATIENT PROFILES

The diagnosis of IDCM was made according to the definition of the World Health Organisation/International Society and Federation of Cardiology task force.<sup>16</sup> Entry criteria was a left ventricular end diastolic diameter > 55 mm in transthoracic M-mode echocardiography, and impaired contraction of the left ventricle with an ejection fraction < 45%. Exclusion criteria were demonstration of valvar heart disease, and coronary macroangiopathy (defined by an epicardial stenoses > 40%), as well as presence of coexisting

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diseases, which might per se lead to an increase in endothelin concentrations as described for renal insufficiency (mean (SD) creatinine concentrations: IDCM 0.97 (0.24) mg/dl *v* controls 0.90 (0.12) mg/dl; NS), hepatic insufficiency (prothrombin time measured in seconds expressed as the international normalised ratio: IDCM 1.16 (0.47) *v* controls 1.00 (0.05); NS), or diabetes mellitus.

Clinically, all patients were characterised according to the New York Heart Association (NYHA) classification. The rate-pressure product was calculated by multiplying heart rate (beats per minute (bpm)) by systolic blood pressure (mm Hg) (Riva-Rocci method after resting for 15 minutes in supine position) on the day of admission. All patients were receiving treatment for heart failure. One patient presented with decompensation eight days before investigation, necessitating treatment adjustment. Medication in the IDCM patients comprised: digitalis in 39% of patients; angiotensin converting enzyme inhibitors in 69%; second generation dihydropyridine calcium antagonists in 31%; diuretics in 31%; nitrates in 31%; and  $\beta$  blockers in 15%. Fourteen patients (eight male/six female) with IDCM were included in the study (NYHA class I–II, *n* = 6; class III, *n* = 8). Five patients (two male/three female) acted as controls. Despite atypical chest pain, none of these subjects was found to have coronary heart disease or evidence of other cardiac diseases after clinical evaluation, including determination of coronary reserve and transvenous endomyocardial biopsy sampling to rule out myocarditis or storage disease. Cardiac index was above 2.5 l/min/m<sup>2</sup> in all controls.

#### ECHOCARDIOGRAPHIC STUDIES

A transthoracic cardiac ultrasound in combined M-mode and two dimensional echocardiography technique was performed using a Toshiba SSH 140. M-mode echocardiography was performed with a 2.25 or 3.5 MHz transducer. M-mode echocardiographic studies were done according to the recommendations of the American Society of Echocardiography, and included measurements of the left ventricular internal dimensions and the thickness of the interventricular septum, as well as the left ventricular posterior wall at end diastole.<sup>17</sup>

#### MEASUREMENT OF CENTRAL HAEMODYNAMICS

Before starting determination of coronary circulation, pressures in the pulmonary artery, pulmonary capillary wedge position, and right atrium, as well as in the aorta, were measured with fluid filled catheters. Cardiac output was determined by thermodilution technique in triplicate and cardiac index was calculated in regard to body surface area. The derived systemic and pulmonary haemodynamic data were calculated as follows:  $SVR = (MAP - RAP) \times 80/CO$ , where SVR is systemic vascular resistance (dyn.s.cm<sup>-5</sup>), MAP is mean arterial pressure (mm Hg), RAP is right atrial pressure (mm Hg), and CO is cardiac output (l/min);  $PVR = (PAP - PCWP) \times 80/CO$ , where PVR is pulmonary vascular resist-

ance (dyn.s.cm<sup>-5</sup>), PAP is mean arterial artery pressure (mm Hg), and PCWP is pulmonary capillary wedge pressure (mm Hg).

Quantitative biplane ventriculography was performed (30° right anterior oblique, 60° left anterior oblique) by injecting 40 ml of non-ionic contrast medium (Ultravist-370, Schering Inc, Berlin, Germany) into the left ventricle through a pigtail catheter at a speed of 12 ml/s. Left ventricular end diastolic (EDV) and end systolic (ESV) volumes were determined semi-automatically by the AVD system (Siemens, Inc, München, Germany), and the left ventricular ejection fraction was calculated as  $(EDV - ESV)/EDV \times 100(\%)$ . In two patients with IDCM ejection fraction could not be determined quantitatively because of profound extrasystole during ventriculography. Ventriculography and coronary angiography, excluding epicardial coronary artery disease defined as > 40% stenoses in each patient, was done between five and seven days before the measurement of coronary haemodynamics.

#### MEASUREMENT OF CORONARY CIRCULATION

Medication was stopped 12 hours before investigation. Coronary blood flow (ml/min/100 g myocardium) was measured under baseline conditions between 09:00 and 10:00 using the inert chromatographic argon gas method. During the investigation all patients were in sinus rhythm. The principle of the argon method is the gas chromatographic determination of the argon concentration of blood samples taken simultaneously from the coronary sinus and the descending aorta while the patient is breathing an oxygen-argon mixture (21% oxygen, 79% argon). The aortic pressure is measured by a fluid filled multipurpose catheter in the descending aorta. Coronary vascular resistance ( $R_{cor}$  (mm Hg.min.100 g myocardium/ml)) was calculated as the coronary perfusion pressure (coronary perfusion pressure = mean systemic arterial pressure – mean right atrial pressure) divided by coronary blood flow. Myocardial oxygen consumption per 100 g myocardium ( $MVO_2$  (ml O<sub>2</sub>/min/100 g myocardium)) was determined as the product of coronary blood flow per unit weight of myocardium and the aortocoronary sinus oxygen content difference ( $acsDO_2$  (vol%)). Advantages and disadvantages of the inert chromatographic argon gas method have been discussed previously.<sup>18</sup> Oxygen saturations ( $SO_2$  (%) = oxygenated haemoglobin  $\times$  100/total haemoglobin) were measured, under inhaled 21% oxygen, from the descending aorta ( $S_aO_2$ ) and from the coronary sinus ( $S_cO_2$ ) with a Radiometer Copenhagen ABL System 600 automated blood and pH analyser. Coronary sinus content of oxygen ( $CscO_2$  (vol%)) was calculated as  $1.34 \times (ml O_2/g \text{ haemoglobin}) \times \text{haemoglobin (g/l)} \times S_cO_2 (\%) \times 10^{-3}$ , while omitting the small contribution of the dissolved oxygen in plasma to the total oxygen content in whole blood samples.

#### BLOOD SAMPLING PROCEDURE AND ENDOTHELIN ASSAYS

EDTA plasma was sampled at the beginning of the investigation from the descending aorta

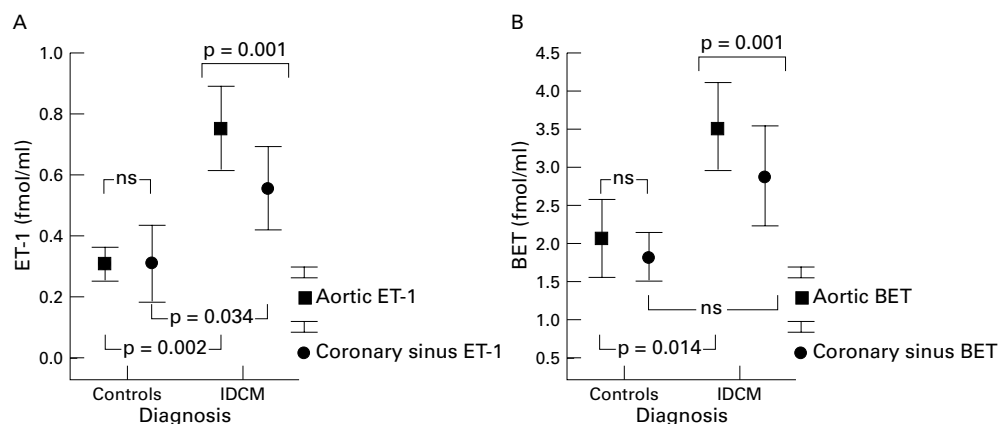


Figure 1 Endothelin-1 (ET-1) concentrations (A) and big endothelin (BET) concentrations (B) for each group from the descending aorta and the coronary sinus (mean (SEM)). In patients with IDCM an aortocoronary sinus gradient suggests a net uptake of ET-1 and BET concentrations in the heart.

(arterial sample) and from the coronary sinus (coronary sinus sample). The samples were immediately stored on ice and centrifuged. Aliquots were stored at  $-80^{\circ}\text{C}$  until further analysis. Lipaemic and/or haemolytic samples were discarded.

Endothelin<sub>1/2</sub> like immunoreactivity was measured using a quantitative radioimmunoassay (Biomedica, Vienna) for endothelin<sub>1/2</sub>.<sup>19</sup> The reactivity with BET is  $< 1\%$ . The sensitivity range is as low as 0.1 fmol/ml. The intra-assay precision and the interassay precision expressed as the coefficient of variance are  $< 3\%$  and  $< 12\%$ , respectively (manufacturer's data).

BET was measured as immunoreactive BET (C-terminal fragment BET) by a commercially available extraction based radioimmunoassay (Biomedica), as described elsewhere in detail.<sup>20</sup> It has 100% reactivity with BET, 82% with a C-terminal fragment of BET, and  $< 1\%$  with endothelin 1, 2, 3. The sensitivity range is 0.7 fmol/ml and the linear range of the calibration curve extends from 1–17 fmol/ml, with an intraassay precision  $< 8\%$  and an interassay precision  $< 13\%$  expressed as the coefficient of variance (manufacturer's data).

The aortocoronary sinus differences of ET-1 (acsD-ET-1 (fmol/ml)) and BET (acsD-BET (fmol/ml)) concentrations were calculated.

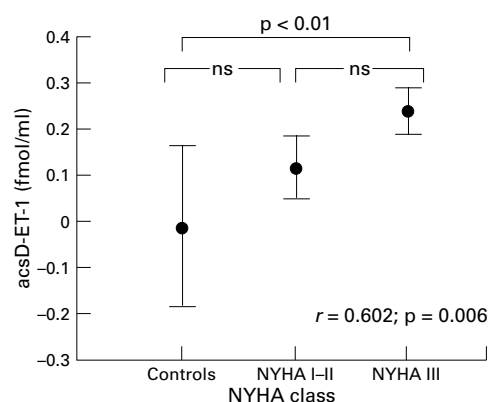


Figure 2 With progression of heart failure the aortocoronary sinus gradient of ET-1 concentration (acsD-ET-1) across the coronary circulation increases (mean (SEM)). The net uptake of ET-1 is significantly increased with NYHA class.

All study patients gave their informed consent. The study protocol was approved by the ethics committee of the Heinrich-Heine University Düsseldorf, Germany, and conformed to the principles of the Declaration of Helsinki.

#### STATISTICS

Descriptive data are expressed as mean (SD) unless otherwise indicated. The Mann-Whitney U test was used to demonstrate group differences between IDCM and controls. The Wilcoxon rank test was applied for statistical analysis of acsD-ET-1 and acsD-BET across the myocardium for paired data in each group. For further analysis, the IDCM group was divided according to functional capacity in patients with NYHA I–II and NYHA III; the latter included the patient with NYHA class IV CHF who had to be recompensated before clinical investigation. A Kruskal-Wallis test with following Bonferroni adjustment for multiple comparison was used for the latter analysis. Correlation analysis was done by Spearman's test. Statistical significance was designated at  $p < 0.05$  for two tailed analysis. An SPSS/PC package Vers. 7.5.2 (SPSS Inc, Chicago, USA) was used for statistical analysis.

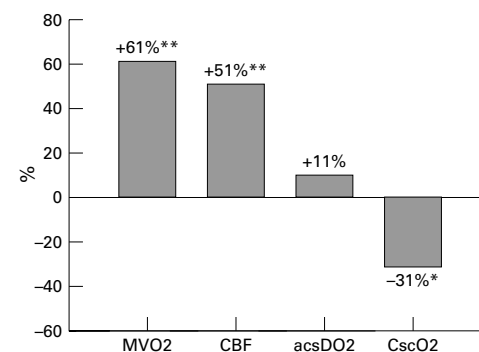


Figure 3 Metabolic demand measured by myocardial oxygen consumption (MVO<sub>2</sub> (ml/min/100 g myocardium)) is increased by 61% (\*\* $p < 0.001$ ) in patients with IDCM compared to controls, whereas coronary blood flow (CBF (ml/min/100 g myocardium)) is only increased by 51% (\*\* $p < 0.001$ ), accompanied by an increased aortocoronary sinus oxygen content difference (acsDO<sub>2</sub> (vol%)) of 11% ( $p = 0.16$ ), caused by a significant decrease of coronary sinus content of oxygen (CscO<sub>2</sub> (vol%)) by 31% (\* $p = 0.003$ ).

Table 1 Functional class data of IDCM patients and controls

	Controls (n = 5)	NYHA I-II (n = 6)	NYHA III (n = 8)
Age (years)	52 (7)	62 (8)	57 (9)
Left ventricular end diastolic diameter (mm)	44 (4)	61 (7)†***	63 (8)†**
End diastolic volume index (ml/m <sup>2</sup> )	96 (35)	153 (40)†**	200 (36)†***
Mean pulmonary artery pressure (mm Hg)	16 (3)	23 (12)	26 (17)
Pulmonary capillary wedge pressure (mmHg)	8 (2)	8 (2)	15 (9)†*
Cardiac index (l/min/m <sup>2</sup> )	3.02 (0.61)	3.42 (0.84)	3.18 (0.68)
Pulmonary vascular resistance (dyn.s.cm <sup>-5</sup> )	126 (34)	175 (138)	166 (143)
Systemic vascular resistance (dyn.s.cm <sup>-5</sup> )	1258 (208)	1144 (291)	1392 (351)
Coronary blood flow (ml/min/100 g myocardium)	68 (8)	100 (26)	108 (38)†*
Rcor at rest (mm Hg.min/100 g myocardium/ml)	1.46 (0.25)	1.07 (0.26)	1.09 (0.29)
MVO <sub>2</sub> (ml O <sub>2</sub> /min/100 g myocardium)	8.52 (1.07)	13.31 (4.16)†*	14.04 (4.18)†**
Coronary sinus oxygen saturation (%)	34 (5)	23 (6)†*	25 (4)†*
Aortocoronary sinus oxygen content difference (vol %)	12.4 (1.18)	14.1 (1.3)	13.3 (1.6)
Coronary sinus content of oxygen (%)	6.7 (1.1)	4.5 (1.3)	4.8 (0.9)
Aortic BET concentrations (fmol/ml)	2.11 (0.58)	3.08 (1.24)	3.96 (0.77)†**
Coronary sinus concentrations BET (fmol/ml)	1.87 (0.37)	2.48 (1.05)	3.31 (1.28)
acsD-BET (fmol/ml)	0.26 (0.44)	0.60 (0.53)	0.65 (0.90)
Aortic ET-1 concentrations (fmol/ml)	0.31 (0.06)	0.65 (0.31)†*	0.85 (0.29)†**
Coronary sinus concentrations ET-1 (fmol/ml)	0.32 (0.14)	0.52 (0.34)	0.61 (0.19)†*
acsD-ET-1 (fmol/ml)	-0.04 (0.20)	0.13 (0.08)	0.24 (0.07)†**

Data are means (SD).

\*p < 0.05; \*\*p < 0.01; \*\*\*p < 0.001; †controls/NYHA I-II; ‡controls/NYHA III.

ET-1, endothelin-1; BET, big endothelin; Rcor, coronary resistance; MVO<sub>2</sub>, myocardial oxygen consumption; acsD, aortocoronary sinus difference.

## Results

Patient groups (IDCM patients *v* controls, respectively) did not differ significantly in regard to age (59 (9) *v* 52 (7) years), heart rate (80 (18) *v* (75) (21) bpm), mean arterial pressure (108 (13) *v* 98 (10) mm Hg), rate-pressure product (12 744 (3698) *v* 10 407 (2863) mm Hg.bpm), haemoglobin

concentrations (14.2 (1.1) *v* 14.6 (1.0) g/dl), and arterial oxygen saturation (96 (2) *v* 98 (1)%). Cardiac index (3.3 (0.73) *v* 3.0 (0.61) l/min/m<sup>2</sup>) as well as systemic vascular resistance (1355 (292) *v* 1258 (208) dyn.s.cm<sup>-5</sup>), and pulmonary vascular resistance (170 (135) *v* 126 (34) dyn.s.cm<sup>-5</sup>) were similar in the patient groups. Ejection fraction was decreased in the IDCM patients compared to controls (36 (9) *v* 67 (7)%; p < 0.001).

Aortic plasma ET-1 (0.76 (0.25) *v* 0.31 (0.06) fmol/ml; p = 0.002), coronary sinus ET-1 (0.57 (0.26) *v* 0.32 (0.14) fmol/ml; p = 0.034), and aortic BET concentrations (3.58 (1.06) *v* 2.11 (0.58) fmol/ml; p = 0.014) were significantly increased in IDCM patients compared with controls, whereas coronary sinus BET was not (2.95 (1.22) *v* 1.87 (0.37) fmol/ml; NS). Patients with IDCM had significantly higher aortic than coronary sinus ET-1 concentrations (0.76 (0.25) *v* 0.57 (0.26) fmol/ml; p = 0.001) and BET concentrations (3.58 (1.06) fmol/ml *v* 2.95 (1.22) fmol/ml; p = 0.001), indicating an aortocoronary sinus gradient across the coronary circulation in IDCM patients, which was not the case in controls (ET-1 0.31 (0.06) *v* 0.32 (0.14) fmol/ml, NS; BET 2.11 (0.58) *v* 1.87 (0.37), NS) (fig 1).

The difference between aortic and coronary sinus ET-1 concentrations (fig 2) was significantly increased with higher NYHA class (r = 0.602; p = 0.006) and pulmonary capillary wedge pressure (r = 0.46, p = 0.046). The difference between aortic and coronary sinus BET concentrations did not correlate with

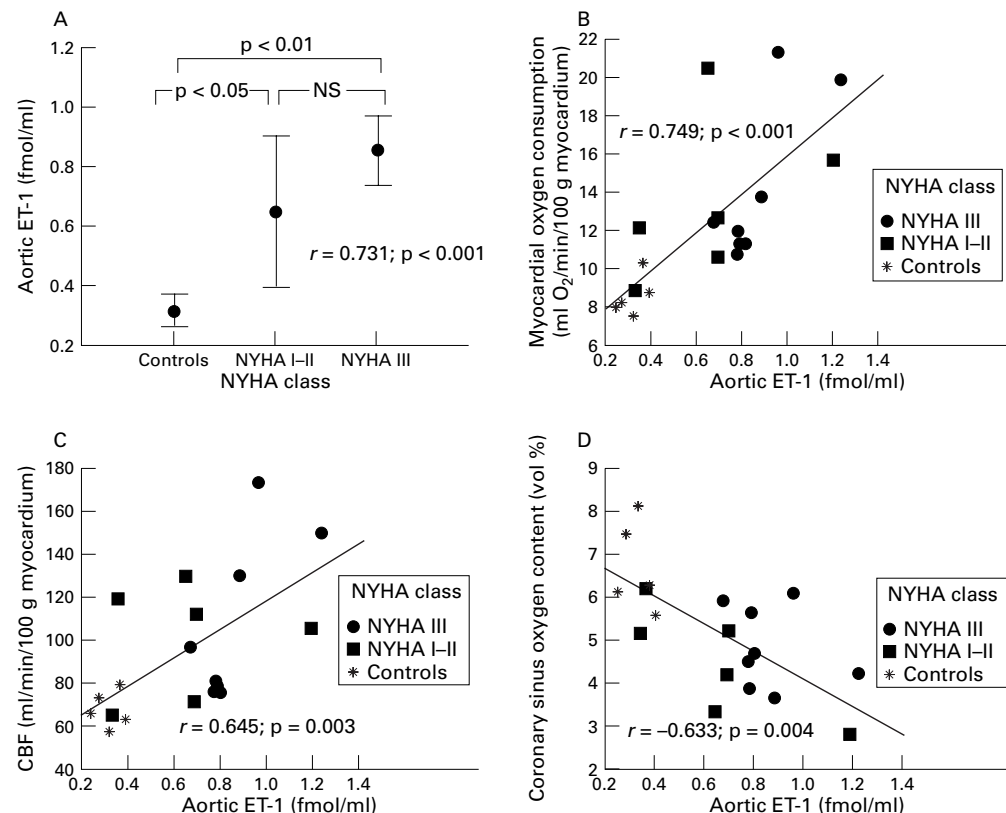


Figure 4 Aortic ET-1 concentration increases with NYHA class (A). Aortic ET-1 is correlated with an increase in myocardial oxygen consumption (MVO<sub>2</sub>) (B), an increase in coronary blood flow (CBF) at rest (C), and a decrease in coronary sinus content of oxygen (CscO<sub>2</sub>) (D).



NYHA class or pulmonary capillary wedge pressure.

Under basal conditions myocardial metabolic demand, as measured by myocardial oxygen consumption, was significantly higher in IDCM patients versus controls ( $13.72 \pm 4.02$  v  $8.52 \pm 1.07$  ml O<sub>2</sub>/min/100 g myocardium,  $p < 0.001$ ) and coronary blood flow was concomitantly increased ( $104 \pm 33$  v  $68 \pm 8$  ml/min/100 g myocardium;  $p < 0.001$ ). Coronary sinus oxygen saturation ( $24 \pm 5$  v  $34 \pm 5$ %;  $p = 0.019$ ) and coronary sinus content of oxygen ( $4.68 \pm 1.05$  v  $6.70 \pm 1.06$  vol%;  $p = 0.003$ ) were decreased in IDCM patients compared with controls (fig 3).

Aortic ET-1 concentration correlated with NYHA class ( $r = 0.731$ ;  $p < 0.001$ ), an increase in left ventricular end diastolic diameter ( $r = 0.521$ ;  $p = 0.022$ ), an increase in end diastolic volume index ( $r = 0.661$ ;  $p = 0.007$ ), and a decrease in ejection fraction ( $r = -0.615$ ;  $p = 0.009$ ). Furthermore, it correlated with an increase in myocardial oxygen consumption ( $r = 0.749$ ;  $p < 0.001$ ) and an increase in coronary blood flow ( $r = 0.645$ ;  $p = 0.003$ ). Myocardial oxygen consumption was inversely correlated with the coronary sinus content of oxygen ( $r = -0.533$ ;  $p = 0.019$ ), the latter being inversely correlated to aortic ET-1 concentrations ( $r = -0.633$ ;  $p = 0.004$ ) (fig 4).

Aortic BET concentrations correlated positively with NYHA class ( $r = 0.764$ ;  $p < 0.001$ ) and negatively with ejection fraction ( $r = -0.736$ ;  $p < 0.001$ ). It correlated with a higher myocardial oxygen consumption ( $r = 0.477$ ;  $p = 0.039$ ), but not with a higher coronary blood flow ( $r = 0.360$ ; NS).

Functional capacity data are shown in table 1.

### Discussion

To the best of our knowledge, this is the first study to demonstrate differences between aortic and coronary sinus endothelin concentrations in IDCM and to link ET-1 and BET plasma concentrations to the coronary circulation in regard to myocardial oxygen demand, coronary sinus oxygen content, and coronary blood flow at basal conditions in patients with IDCM.

As stated by other investigators,<sup>4-8</sup> we found that in patients with IDCM with increasing NYHA class the plasma concentrations of immunoreactive ET-1/BET in arterial samples were increased. This was correlated with an increase in internal left ventricular dimensions and a decreased ejection fraction. An increment of ET-1/BET concentrations in venous samples of patients with CHF was described by Pacher *et al* and Pousset *et al* to be of prognostic importance, independent from haemodynamic data in patients with CHF.<sup>7,8</sup> Therefore, our results are in accordance with the hypothesis that, with progressive heart failure, the endothelin system is activated.

In our study, the aortocoronary sinus difference of ET-1 concentration was increasing with higher NYHA class in IDCM patients, indicating an aortocoronary sinus gradient for the vasoactive ET-1, but not for the biologically rather inert precursor BET. Although supposed

to act predominantly in an autocrine or paracrine fashion, plasma endothelin concentrations have been reported to be increased in CHF.<sup>4-8</sup> Genes encoding for ET-1 can be detected in a wide variety of tissues, including endothelial and smooth muscle cells of blood vessels, heart, brain, kidney, pancreas, spleen, and lung.<sup>21</sup> The lung might be of exceptional importance for raising plasma endothelin immunoreactivity in the setting of CHF. Cody *et al* found a correlation of pulmonary hypertension and plasma endothelin concentrations in patients with CHF.<sup>22</sup> Tsutamato *et al* showed that the main source of circulating ET-1 in CHF was the pulmonary vascular bed.<sup>23</sup> Mechanisms which lead to an increased spillover of ET-1 from the lung into the systemic circulation might include an increased production or a decreased pulmonary clearance of ET-1 in the lung.<sup>24-26</sup> An increase in left atrial pressure or pulmonary capillary wedge pressure was found to be correlated with an increased endothelin spillover from the lung in mitral stenosis.<sup>27</sup> Thus, an altered endothelin metabolism within the lung in chronic heart disease might expose the coronary circulation to a higher ET-1 burden by increasing aortic ET-1 concentrations.

It is still not clear whether increased circulating ET-1 is a marker or a mediator of disease in CHF. White *et al* reported a reduced coronary sinus oxygen content in patients with severe CHF, that was a predictor of increased mortality.<sup>28</sup> Myocardial oxygen consumption is closely related to heart rate, the inotropic status of the heart, and an increase in wall stress caused by a dilatation of the ventricle with relative or absolute wall thinning in IDCM. Myocardial oxygen consumption at basal conditions was significantly increased in our patients with IDCM. This is indicative of an increased metabolic demand even in the absence of an increased pulmonary or systemic vascular resistance, excluding an increased afterload. In the normal heart an increased metabolic demand is physiologically met by a parallel increase in coronary blood flow.<sup>29</sup> The higher metabolic demand in IDCM was not completely matched by an adequate rise in coronary blood flow at basal conditions, which becomes obvious by a compensatory increase of the aortocoronary sinus difference resulting in a significant decrease in the coronary sinus content of oxygen. Similar results have been reported by de Marco *et al* in patients with ischaemic and non-ischaemic heart failure.<sup>30</sup> The relative imbalance between increased myocardial oxygen demand and inadequately augmented coronary blood flow under basal conditions was associated with an increase in aortic plasma ET-1 concentrations and might be explained by the vasoconstrictive effects of ET-1. Hence, an activated endothelin system could have a pathophysiological effect on the coronary circulation that might counteract vasodilating mechanisms.

The best known and investigated effect of ET-1 is its vasoconstrictive action. It is the most potent endogenous vasoconstrictor known. Endothelin acts primarily via two different

receptor subtypes, namely ET-A and ET-B. The latter might be further subdivided into ET-B<sub>1</sub> receptors, which are localised mainly on endothelial cells, and ET-B<sub>2</sub> receptors, which have been found on vascular smooth muscle cells. Whereas the ET-A receptor and ET-B<sub>2</sub> receptor elicit vasoconstriction, ET-B<sub>1</sub> receptor stimulation induces release of prostacyclin and nitric oxide, which results in short term vasodilation. However, the effect of vasoconstriction seems to outweigh the short term effect of vasodilation,<sup>15</sup> at least in healthy subjects. In contrast to the physiological effect in healthy humans, the endothelin receptor subtype population might be altered in chronic states of heart failure. Cannan *et al* demonstrated in a model of low cardiac output an attenuated vasoconstrictor response to ET-1 and an enhanced vasoconstriction by sarafatoxin 6b, an endothelin B receptor agonist, which suggests a modification in coronary ET receptor sensitivity in experimental heart failure.<sup>31</sup> Nevertheless, the effect of ET-1 was still vasoconstriction, although this may be mediated by ET-B<sub>2</sub> receptors. Taking into account the interrelation between endothelin and various other vasoactive endothelial substances, including vasodilating nitric oxide, coronary blood flow could therefore be adversely influenced by the vasoconstrictive effects of ET-1 via ET-A or ET-B<sub>2</sub> receptors.<sup>32 33</sup>

In conclusion, in patients with IDCM the endogenous plasma endothelin system is activated and might influence coronary circulation. As reported in other studies we demonstrated a correlation of ET-1 plasma concentrations with functional NYHA class. Furthermore, ET-1 plasma concentrations were found to be associated with an increased metabolic demand and a decreased coronary sinus oxygen content, despite an increased coronary blood flow under basal conditions in patients with IDCM.

Functional impairment of cardiac contractility and metabolism can be detected early in the course of heart disease, while systemic haemodynamic parameters at basal conditions are still in the normal range. We could demonstrate that ET-1 and BET concentrations are higher in the aorta than in the coronary sinus in IDCM. Although we could not distinguish between consumption and production of endothelin in the heart, which would require an indicator-dilution technique, our findings imply a net uptake of receptor bound endothelin in the heart. Haemodynamic data from IDCM patients were not significantly altered in comparison with controls, indicating that all patients were compensated in regard to systemic circulation under reported medication for heart failure. As ET-1 exerts a positive inotropic effect on the heart,<sup>34 35</sup> it is speculated that increased availability of circulating endothelin represents some form of compensatory mechanism in heart failure. Further studies are needed to investigate this implication in IDCM.

Thus, ET-1 plasma concentration seems to be a more sensitive indicator of deteriorated myocardial function than baseline haemodynamic data. Although the mechanisms leading to an increased ET-1 plasma concentration in

heart failure are not clear, an increased ET-1 burden to the coronary circulation, which can counteract coronary vasodilation, might result in the observed inadequate upregulation of coronary blood flow in relation to metabolic demand. It is hypothesised that this represents a link between an activated endothelin system and a progression of heart failure.

#### LIMITATIONS OF THE STUDY

We did not simultaneously investigate other neurohumoral factors, which are known to be involved in the activation of the cardiovascular system in CHF. We are therefore aware that further studies are required to clarify the complex interactions between endothelins, the renin angiotensin system, the sympathetic-adrenergic system, nitric oxide, and various other factors which might influence coronary circulation.

A presumed direct vasodilating action of endothelin via ET-B<sub>1</sub> in chronic heart disease cannot be ruled out definitely by our study. Hence, localisation of receptor subtypes in the myocardium is needed to clarify the direct actions of endothelin on the myocardial vascular bed. Furthermore, pharmacological receptor antagonist studies would improve the understanding of the role of endothelin and its different receptor subtypes in regard to coronary circulation.

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